XON11, a novel multi-target antibody in pancreas cancer

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Background: Pancreatic cancer continues to be one of the most lethal cancer types, with a 5-year overall survival rate of only 12%. It poses one of the toughest challenges in oncology, as chemotherapy and immunotherapy have not significantly improved patient outcomes. Consequently, there is an urgent need for new therapeutic approaches. XON11 is a new polyclonal antibody targeting several pancreatic cancer antigens, including KrasG12D. The aim of these studies was to assess the tolerance and efficacy of XON11 in non-clinical pancreatic cancer models.

Material and methods: XON11 ability to induce Complement Dependent Cytotoxicity (CDC) and apoptosis compared to gemcitabine was tested in a panel of human pancreas cancer cell (MiaPaca, Aspc1, Capan, Panc1) after 24h of incubation. The capacity of XON11 and gemcitabine to impair tumorsphere formation and growth was investigated in pancreatic cancer cells for 11 days. In vivo XON11 and gemcitabine tolerance and efficacy was evaluated in NMRI nude mice after intraperitoneal dosing at 40 mg/kg tri-weekly for 4 weeks.

Results: XON11 showed potent and selective anti-proliferative activity in a panel of human pancreatic Kras muted cancer cell lines, including those resistant to gemcitabine. It induced specific tumor cell cytotoxicity (Mean EC50 = 25.85 µg/mL) without affecting healthy cells (PBMC) at this concentration. XON11 displayed significantly higher potency against pancreatic cancers compared to gemcitabine. It was able to kill up to 97% of the cancer cells, whereas gemcitabine's maximum effect reached 30%. XON11 induced both caspase 8 and caspase 9 (suggesting activation of both apoptosis pathways). Furthermore, it induced a dose- response loss of mitochondrial membrane potential and ROS generation in different pancreatic cell lines. In contrast to gemcitabine, XON11 significantly decreased Aspc1 tumorspheres viability after treatment (>75% of cytotoxicity). In addition, XON11 completely inhibited sphere formation from 33µg/ml. XON11 was significantly effective against tumor growth in two xenograft mouse models and well tolerated in mice after repeated intraperitoneal dosing at 40 mg/kg over 28 days.

Conclusion: Based on its high potency and tolerance, XON11 can provide a novel and promising therapy for fighting recurrent pancreatic cancer.

Keywords: Pancreas cancer, Immunotherapy, resistance

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XENOTHERA

INTRODUCTION

Pancreatic cancer continues to be one of the most lethal cancer types, with a 5-year overall survival rate of only 12%. It is one of the greatest challenges in oncology, as chemotherapy and immunotherapy have not significantly improved patient outcomes. Therefore, there is an urgent need for new therapeutic approaches.

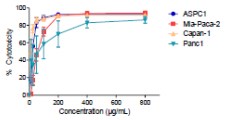
XON11 is a new polyclonal antibody targeting several pancreatic cancer antigens, including KrasG12D. The aim of these studies was to assess the tolerance and efficacy of XON11 in non-clinical pancreatic cancer models.

MATERIAL AND METHODS

- XON11 is obtained by hyperimmunizing rabbits with tumoral antigens
- KRAS mutation in pancreatic adenocarcinoma cell lines tested:
  - ASPC1: KRAS G12D
  - Mia-Paca-2: KRAS G12C
  - Capan-1: KRAS G12V
  - Panc1: KRAS G12D
- ***In vitro Assays***
  - Anti-tumor activity was assessed in a panel of pancreatic cell lines in a complement dependent cytotoxicity assay in presence of rabbit complement (1:3) and serial dilution of XON11 after 1h or 24h of incubation.
  - Apoptotic assay was performed on ASPC1 cell line in presence of increased concentrations of XON11 (0, 30, 100 and 300 µg/ml) and labelled with AF488-conjugated Annexin V after 24h of incubation
  - 3D culture of ASPC1 have been developed to study repeated administrations of XON11 and tumorigenicity.
- ***In vivo studies***
  - Pancreatic adenocarcinoma xenografts were established by subcutaneous injection of 5×10^6 ASPC1 or BXPC3 cells in 50% Matrigel. Treatment with XON11 or gemcitabine (40 mg/kg, i.p.) was initiated when tumors reached ~50 mm^3 and administered three times per week. Tumor progression was monitored by volume measurement. volume.

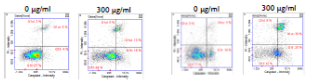
RESULTS

XON11 induces a potent anti tumoral activity against a panel of pancreatic cancer cell lines (CellTiter-Glo 24h)



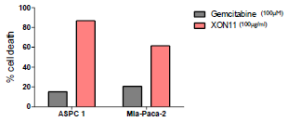
After 24 hours incubation with serial dilutions of XON11 and in the presence of rabbit complement, XON11 induced cytotoxic activity ranging from 70% for the least sensitive cell line to 90% for the other cell lines.

XON11 induces apoptosis via both pathways: intrinsic and extrinsic as shown by Caspases 8 and 9 activations

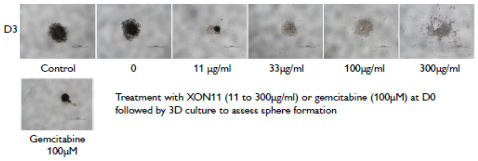


Caspase 8 Caspase 9

XON11 induces tumor cell death even in pancreatic cell line resistant to gemcitabine (CellTiter-Glo 24h)



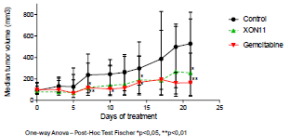
XON11 reduces the tumorogenicity of ASPC1 cells , unlike gemcitabine, by blocking sphere formation



Treatment with XON11 (11 to 300µg/ml) or gemcitabine (100µM) at D0 followed by 3D culture to assess sphere formation

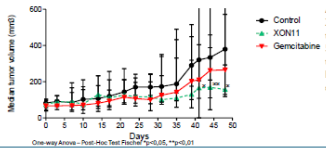
XON11 is effective and well tolerated in PDAC xenograft mice models

ASPC1 Xenograft model



XON11 reduces tumor growth by over 50% after 3 weeks of treatment, with no signs of associated toxicity. In contrast, a 20% mortality rate was observed in the gemcitabine-treated group, highlighting the toxicity of gemcitabine at this dose.

BXPC3 Xenograft model



After 45 days of treatment, XON11 induced a significant tumor volume reduction of over 50%. Gemcitabine showed a trend toward tumor reduction, but the effect was not statistically significant.

REFERENCE

To learn more about polyclonal antibodies in oncology:
Ciron et al. JCI Insight 2024 Feb 8;9(3)

Poster high resolution

CONCLUSION

- XON11 displays higher potency against pancreatic cancers compared to Gemcitabine
- XON11 acts via 2 main modes of action: CDC and apoptosis, with activation of both intrinsic and extrinsic pathways
- XON11 reduces the tumorogenicity of pancreas cancer cell line ASPC1, by blocking spheroid formation
- XON11 reduces pancreas tumor growth in xenograft model after 3 weeks of treatment with no associated toxicity

XON11 can provide a novel and promising therapy for fighting recurrent pancreatic cancer

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